DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Addendum to the FDA Briefing Document
Endocrinologic and Metabolic Drugs Advisory Committee Meeting
May 10, 2012

I. Cardiovascular Risk Assessment

A. Background

FDA convened an advisory committee March 28-29, 2012, to discuss the cardiovascular (CV) safety requirements for obesity drug approval. This meeting was designed to be similar to the FDA advisory committee held in July 2008 to discuss the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus.

The guidance for developing new drugs or biologics for the treatment of type 2 diabetes[1], issued subsequent to the 2008 meeting, recommends that pharmaceutical companies show that their therapies do not result in an unacceptable increase in cardiovascular risk. This recommendation applies to products that do not have a signal of cardiovascular harm in non-clinical or clinical studies.

The March 2012 advisory committee recommended that sponsors of obesity drugs without a theoretical risk or signal for CV harm should be required to rule out a certain degree of excess CV risk prior to approval.

Lorcaserin was developed prior to the discussions regarding obesity drug CV risk assessments. Therefore, trials were not designed to capture and evaluate CV events; the background risk of CV events was relatively low and there was no procedure set up for prospective adjudication.

However, in light of the recent advisory committee meeting discussion, FDA has conducted several analyses of the unadjudicated CV adverse events collected in the phase 3 trials. In addition, FDA has calculated the relative risk with 95% CI of the sponsor's post-hoc blinded adjudication (by an independent committee) of major adverse cardiovascular events (MACE) from the BLOOM and BLOSSOM trials (Table 7).

1 Guidance for industry: Diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. In: Guidances (drugs). United States Food and Drug Administration. 2008. http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/ucm071627.pdf. Accessed 13 Jan 2012.

B. Methods

FDA CV Event Search

Because the adverse events were not prospectively adjudicated, nor was there a procedure for internal post-hoc adjudication, we felt that utilizing a listing of prespecified preferred terms within a particular topic of interest with Standardized MedDRA[2] Queries (SMQs) for assessment of CV risk would be a reasonable approach. Table 1 demonstrates the SMQs that were considered for these analyses. More narrow SMQs are subsumed by broader SMQs as one moves to the left in the table.

Table 1. Standardized MedDRA Queries Considered for CV Risk Analyses

Cerebrovascular Disorders SMQ	Central nervous system haemorrhages and cerebrovascular conditions SMQ	Conditions associated with central nervous system haemorrhages and cerebrovascular accidents SMQ (includes terms such as dysarthria and paralysis)
		Haemorrhagic cerebrovascular conditions SMQ
		Ischaemic cerebrovascular conditions SMQ (includes cerebrovascular accident (stroke) and transient ischemic attack)
	Cerebrovascular disorders, not specified as haemorrhagic or ischaemic SMQ (includes vasculitis and sinus thrombosis)	
Ischaemic heart disease SMQ	Myocardial infarction SMQ	
	Other ischaemic heart disease SMQ (includes angina, arteriosclerosis, angioplasty)	
MedDRA version 14.1		

We chose a "broad" group of terms to encompass a spectrum of possible ischemic cardiac and cerebrovascular events, and a "narrow" group of terms that parallels a stricter MACE definition (see Table 2). We also evaluated the following SMQs separately (please see the Appendix): Cerebrovascular Disorders SMQ (in the lorcaserin database, these terms were equivalent to those in the Central nervous system haemorrhages and cerebrovascular conditions SMQ); Ischaemic cerebrovascular conditions SMQ; Ischaemic heart disease SMQ; and Myocardial infarction SMQ.

Although there were some terms/cases that were not likely associated with a CV event (e.g., intracranial hemorrhage due to trauma), no attempt was made by FDA to alter the SMQ by adding or subtracting terms or cases, since we were not adjudicating all cases. .

2 MedDRA - the Medical Dictionary for Regulatory Activities - is a medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products. http://www.meddramsso.com Accessed 23 April 2012.

Table 2. Broad and Narrow Grouping of SMQs

BROAD	**NARROW**
Haemorrhagic cerebrovascular conditions SMQ	Ischaemic cerebrovascular conditions SMQ
Ischaemic cerebrovascular conditions SMQ	Myocardial infarction SMQ
Ischaemic heart disease SMQ	

Sponsor's Post-hoc CV Event Adjudication

As described in the FDA clinical briefing document, cardiovascular events from BLOOM and BLOSSOM were independently adjudicated in a post-hoc fashion. BLOOM-DM events were not included.

The adjudication process was conducted by an independent committee (the Cardiovascular Clinical Events Committee (CCEC)) consisting of physicians from the Brigham and Women's Hospital (Boston, Massachusetts).

The goal of the CCEC was to define and adjudicate the following potential endpoints from BLOOM and BLOSSOM in a consistent and unbiased manner (in essence, MACE-plus):

- Cardiovascular Death
- Cardiovascular Ischemic Events including myocardial infarction and hospitalization for unstable angina
- Cerebrovascular Events including stroke and transient ischemic attack

The sponsor was responsible for identifying potential events from BLOOM and BLOSSOM for review. Potential events were triggered by either (1) death of a subject, (2) report of a serious adverse event (SAE) with a preferred term of chest pain or chest discomfort, or (3) a SAE meeting any of the specific terms in the Ischaemic heart disease SMQ (including the Myocardial infarction SMQ, Other ischaemic heart disease SMQ), Ischaemic cerebrovascular conditions SMQ, and Conditions associated with central nervous system haemorrhages and cerebrovascular accidents SMQ.

The two physician reviewers were to independently review the cases assigned to them, document and provide supporting information for each event's adjudication directly on the endpoint form, and were responsible for bringing their assigned cases with them to a scheduled review session. At this session, the two physicians that were assigned to each case reviewed the event together and compare adjudications. If the two adjudications agreed on all data fields, the event was considered complete and a single form was signed by both reviewers. If there was initial disagreement and if after discussion, consensus between the two reviewers was reached on a final adjudication, a single form was signed by both reviewers and represented the final adjudication. If after discussion, no consensus was reached, the case would be presented to a third reviewer for final

adjudication and a single form would be submitted with all three signatures indicating a final adjudication. See the Appendix for a description of endpoint definitions.

C. Results[3]

FDA CV Event Search

Table 3. Broad Search, All Adverse Events

Adverse Events in Broad[3] CV Search

		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio[1] (95% CI)	Odds Ratio[2] (95% CI)	Mantel-Haenszel OR[1]	Mantel-Haenszel OR[2]
BLOOM	Pbo	1584	8	5.05	1.37 (0.55, 3.41)	1.37 (0.55, 3.41)	1.08 (0.61, 1.91)	1.09 (0.64, 1.88)
	Lorc 10 BID	1593	11	6.91				
BLOOM-DM	Pbo	252	8	31.75	0.61 (0.20, 1.88)	0.89 (0.35, 2.30)		
	Lorc 10 BID	256	5	19.53				
	Lorc 10 QD	95	5	52.63				
BLOSSOM	Pbo	1601	7	4.37	1.29 (0.48, 3.46)	1.05 (0.41, 2.71)		
	Lorc 10 BID	1602	9	5.62				
	Lorc 10 QD	801	2	2.50				

[1]Lorcaserin 10mg BID vs placebo. [2]All lorcaserin vs placebo
[3]Broad Search includes: Haemorrhagic cerebrovascular conditions SMQ, Ischaemic cerebrovascular conditions SMQ and Ischaemic heart disease SMQ

3 All analyses conducted by Dr. Eugenio Andraca-Carrera, FDA, Office of Biostatistics, DB7

Table 4. Broad Search, Serious Adverse Events Only

Serious Adverse Events in Broad[3] CV Search

		Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio[1] (95% CI)	Odds Ratio[2] (95% CI)	Mantel-Haenszel OR[1]	Mantel-Haenszel OR[2]
BLOOM	Pbo	1584	3	1.89	0.99 (0.20, 4.93)	0.99 (0.20, 4.93)	1.11 (0.45, 2.73)	1.26 (0.55, 2.90)
	Lorc 10 BID	1593	3	1.88				
BLOOM-DM	Pbo	252	2	7.94	0.49 (0.04, 5.44)	1.81 (0.35, 9.39)		
	Lorc 10 BID	256	1	3.91				
	Lorc 10 QD	95	4	42.11				
BLOSSOM	Pbo	1601	4	2.50	1.50 (0.42, 5.33)	1.17 (0.34, 3.99)		
	Lorc 10 BID	1602	6	3.75				
	Lorc 10 QD	801	1	1.25				

[1]Lorcaserin 10mg BID vs placebo. [2]All lorcaserin vs placebo

[3]Broad Search includes: Haemorrhagic cerebrovascular conditions SMQ, Ischaemic cerebrovascular conditions SMQ and Ischaemic heart disease SMQ

Table 5. Narrow Search, All Adverse Events

Adverse Events in Narrow[3] CV Search

		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio[1] (95% CI)	Odds Ratio[2] (95% CI)	Mantel-Haenszel OR[1]	Mantel-Haenszel OR[2]
BLOOM	Pbo	1584	7	4.42	0.57 (0.17, 1.94)	0.57 (0.17, 1.94)	0.78 (0.40, 1.54)	0.77 (0.40, 1.46)
	Lorc 10 BID	1593	4	2.51				
BLOOM-DM	Pbo	252	7	27.78	0.70 (0.22, 2.23)	0.82 (0.29, 2.28)		
	Lorc 10 BID	256	5	19.53				
	Lorc 10 QD	95	3	31.58				
BLOSSOM	Pbo	1601	5	3.12	1.20 (0.37, 3.94)	0.93 (0.30, 2.94)		
	Lorc 10 BID	1602	6	3.75				
	Lorc 10 QD	801	1	1.25				

[1]Lorcaserin 10mg BID vs placebo. [2]All lorcaserin vs placebo

[3]Narrow Search includes: Ischaemic cerebrovascular conditions SMQ, Myocardial infarction SMQ

Table 6. Narrow Search, Serious Adverse Events Only

Serious Adverse Events in Narrow[3] CV Search

		Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio[1] (95% CI)	Odds Ratio[2] (95% CI)	Mantel-Haenszel OR[1]	Mantel-Haenszel OR[2]
BLOOM	Pbo	1584	3	1.89	0.33 (0.03, 3.19)	0.33 (0.03, 3.19)	0.99 (0.35, 2.84)	1.07 (0.40, 2.87)
	Lorc 10 BID	1593	1	0.63				
BLOOM-DM	Pbo	252	2	7.94	0.49 (0.04, 5.44)	1.08 (0.18, 6.50)		
	Lorc 10 BID	256	1	3.91				
	Lorc 10 QD	95	2	21.05				
BLOSSOM	Pbo	1601	2	1.25	2.50 (0.48, 12.93)	2.00 (0.40, 9.93)		
	Lorc 10 BID	1602	5	3.12				
	Lorc 10 QD	801	1	1.25				

[1]Lorcaserin 10mg BID vs placebo. [2]All lorcaserin vs placebo

[3]Narrow Search includes: Ischaemic cerebrovascular conditions SMQ, Myocardial infarction SMQ

Sponsor's Post-hoc CV Event Adjudication

The CCEC received a total of 25 cases blind to treatment assignment for adjudication including 19 potential ischemic events, four potential cerebrovascular events, and two deaths. The two physician reviewers reportedly found the documents provided adequate to adjudicate all cases and reached consensus on all cases.

Overall, 19 potential ischemic event cases yielded five myocardial infarctions, four hospitalizations for unstable angina, and 10 events that did not formally meet either of these criteria. Of the four potential cerebrovascular events, the reviewers coded one stroke, two transient ischemic attacks, and one event that did not formally meet either of these definitions. Both deaths were felt to be non-cardiovascular in nature, with one coded as pulmonary cause, and the other as accident/trauma.

The sponsor unblinded the adjudications, with the results as follows: five lorcaserin 10 mg BID, zero lorcaserin 10 mg QD, six placebo, and one lorc/pbo (Year 2).

The following table exhibits FDA's statistical analysis of the adjudicated CV events in Year 1.

Table 7. Post-Hoc Adjudication of MACE-Plus in BLOOM and BLOSSOM, Year 1

		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio[1] (95% CI)	Mantel-Haenszel OR[1]
BLOOM	Pbo	1584	3[a]	1.89	0.33 (0.03, 3.19)	0.63 (0.19, 2.12)
	Lorc 10 BID	1593	1[b]	0.63		
BLOSSOM	Pbo	1601	3[a]	1.87	0.89 (0.20, 3.97)	
	Lorc 10 BID	1602	4[b]	2.50		
	Lorc 10 QD	801	0	0.00		

1 All lorcaserin vs. placebo
a Placebo events consisted of: 2 unstable angina, 1 MI-silent, 1 stroke, ischemic, and 2 TIA
b Lorcaserin 10 mg BID events consisted of 1 unstable angina and 4 MI-spontaneous

II. Echocardiogram analyses

Because the primary efficacy analysis for FDA-defined valvular heart disease (VHD) was under-powered to rule out a relative risk of more than 1.5 times placebo, the sponsor conducted additional post-hoc analyses that utilized all echocardiographic data through Week 104 and included enough events of FDA-defined VHD to provide at least 80% power for risk ratio assessments. These analyses are included in the table below, with models that adjust for treatment only, as well as analyses that are additionally adjusted by treatment x year (Cox Proportional Hazards) and study (Piecewise Exponential Model and Generalized Estimating Equations).

Table 8. Summary of Echocardiographic Analyses for Proportion of Patients with FDA-defined VHD: Pooled Phase 3 Trials, Lorcaserin 10 mg BID versus Placebo

Method	Model	Parameter	Estimate	95% CI
Cox Proportional Hazards stratified by study	Treatment, Treatment x Year	Hazards Ratio	1.13	(0.84, 1.51)
Cox Proportional Hazards stratified by study	Treatment	Hazards Ratio	1.09	(0.83, 1.44)
Piecewise Exponential Model	Full model, adjusting for Study	Hazards Ratio	1.10	(0.82, 1.48)
Piecewise Exponential Model	Adjusting for TRT only. Not for Study	Hazards Ratio	1.09	(0.82, 1.43)
Generalized Estimating Equations	Full model, adjusting for Study	Rate Ratio	1.12	(0.84, 1.499)
Generalized Estimating Equations	Adjusting for TRT only. Not for Study	Rate Ratio	1.08	(0.81, 1.44)

Note: These supplementary analyses use data for Years 1 and 2.

Appendix.

1. Cerebrovascular Disorders SMQ

Adverse Events in Cerebrovascular Disorders SMQ

		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio[1] (95% CI)	Odds Ratio[2] (95% CI)	Mantel-Haenszel OR[1]	Mantel-Haenszel OR[2]
BLOOM	Pbo	1584	2	1.26	0.99 (0.14, 7.07)	0.99 (0.14, 7.07)	0.75 (0.26, 2.15)	0.84 (0.32, 2.18)
	Lorc 10 BID	1593	2	1.26				
BLOOM-DM	Pbo	252	1	3.97	0.98 (0.06, 15.82)	2.16 (0.22, 20.92)		
	Lorc 10 BID	256	1	3.91				
	Lorc 10 QD	95	2	21.05				
BLOSSOM	Pbo	1601	5	3.12	0.60 (0.14, 2.51)	0.53 (0.14, 1.99)		
	Lorc 10 BID	1602	3	1.87				
	Lorc 10 QD	801	1	1.25				

[1]Lorcaserin 10mg BID vs placebo

[2]All lorcaserin vs placebo

Serious Adverse Events in Cerebrovascular Disorders SMQ

		Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio[1] (95% CI)	Odds Ratio[2] (95% CI)	Mantel-Haenszel OR[1]	Mantel-Haenszel OR[2]
BLOOM	Pbo	1584	1	0.63	0.99 (0.06, 15.91)	0.99 (0.06, 15.91)	0.25 (0.03, 2.23)	0.75 (0.19, 2.99)
	Lorc 10 BID	1593	1	0.63				
BLOOM-DM	Pbo	252	0	0.00	-	-		
	Lorc 10 BID	256	0	0.00				
	Lorc 10 QD	95	2	21.05				
BLOSSOM	Pbo	1601	3	1.87	-	0.22 (0.02, 2.13)		
	Lorc 10 BID	1602	0	0.00				
	Lorc 10 QD	801	1	1.25				

[1]Lorcaserin 10mg BID vs placebo

[2]All lorcaserin vs placebo

2. Ischaemic cerebrovascular conditions SMQ

Adverse Events in Ischaemic cerebrovascular conditions SMQ

		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio[1] (95% CI)	Odds Ratio[2] (95% CI)	Mantel-Haenszel OR[1]	Mantel-Haenszel OR[2]
BLOOM	Pbo	1584	2	1.26	-	-	0.14 (0.02, 1.16)	0.41 (0.12, 1.42)
	Lorc 10 BID	1593	0	0.00				
BLOOM-DM	Pbo	252	1	3.97	-	1.44 (0.13, 15.95)		
	Lorc 10 BID	256	0	0.00				
	Lorc 10 QD	95	2	21.05				
BLOSSOM	Pbo	1601	4	2.50	0.25 (0.03, 2.23)	0.33 (0.06, 1.82)		
	Lorc 10 BID	1602	1	0.62				
	Lorc 10 QD	801	1	1.25				

[1]Lorcaserin 10mg BID vs placebo

[2]All lorcaserin vs placebo

Serious Adverse Events in Ischaemic cerebrovascular conditions SMQ

		Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio[1] (95% CI)	Odds Ratio[2] (95% CI)	Mantel-Haenszel OR[1]	Mantel-Haenszel OR[2]
BLOOM	Pbo	1584	1	0.63	-	-	-	0.73 (0.14, 3.66)
	Lorc 10 BID	1593	0	0.00				
BLOOM-DM	Pbo	252	0	0.00	-	-		
	Lorc 10 BID	256	0	0.00				
	Lorc 10 QD	95	2	21.05				
BLOSSOM	Pbo	1601	2	1.25	-	0.33 (0.03, 3.67)		
	Lorc 10 BID	1602	0	0.00				
	Lorc 10 QD	801	1	1.25				

[1]Lorcaserin 10mg BID vs placebo

[2]All lorcaserin vs placebo

3. Ischaemic heart disease SMQ

Adverse Events in Ischaemic heart disease SMQ

		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio[1] (95% CI)	Odds Ratio[2] (95% CI)	Mantel-Haenszel OR[1]	Mantel-Haenszel OR[2]
BLOOM	Pbo	1584	6	3.79	1.66 (0.60, 4.58)	1.66 (0.60, 4.58)	1.53 (0.79, 2.94)	1.45 (0.77, 2.73)
	Lorc 10 BID	1593	10	6.28				
BLOOM-DM	Pbo	252	7	27.78	0.7 (0.22, 2.23)	0.82 (0.29, 2.28)		
	Lorc 10 BID	256	5	19.53				
	Lorc 10 QD	95	3	31.58				
BLOSSOM	Pbo	1601	2	1.25	4.01 (0.85, 18.92)	3.01 (0.65, 13.93)		
	Lorc 10 BID	1602	8	4.99				
	Lorc 10 QD	801	1	1.25				

[1]Lorcaserin 10mg BID vs placebo

[2]All lorcaserin vs placebo

Serious Adverse Events in Ischaemic heart disease SMQ

		Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio[1] (95% CI)	Odds Ratio[2] (95% CI)	Mantel-Haenszel OR[1]	Mantel-Haenszel OR[2]
BLOOM	Pbo	1584	2	1.26	0.99 (0.14, 7.07)	0.99 (0.14, 7.07)	1.79 (0.60, 5.35)	1.68 (0.58, 4.92)
	Lorc 10 BID	1593	2	1.26				
BLOOM-DM	Pbo	252	2	7.94	0.49 (0.04, 5.44)	1.08 (0.18, 6.50)		
	Lorc 10 BID	256	1	3.91				
	Lorc 10 QD	95	2	21.05				
BLOSSOM	Pbo	1601	1	0.62	6.02 (0.72, 50.02)	4.01 (0.48, 33.30)		
	Lorc 10 BID	1602	6	3.75				
	Lorc 10 QD	801	0	0.00				

[1]Lorcaserin 10mg BID vs placebo

[2]All lorcaserin vs placebo

4. Myocardial infarction SMQ

Adverse Events in Myocardial infarction SMQ

		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio[1] (95% CI)	Odds Ratio[2] (95% CI)	Mantel-Haenszel OR[1]	Mantel-Haenszel OR[2]
BLOOM	Pbo	1584	5	3.16	0.80 (0.21, 2.97)	0.80 (0.21, 2.97)	1.16 (0.53, 2.51)	0.98 (0.46, 2.13)
	Lorc 10 BID	1593	4	2.51				
BLOOM-DM	Pbo	252	6	23.81	0.82 (0.25, 2.71)	0.71 (0.23, 2.24)		
	Lorc 10 BID	256	5	19.53				
	Lorc 10 QD	95	1	10.53				
BLOSSOM	Pbo	1601	1	0.62	5.01 (0.58, 42.93)	3.34 (0.39, 28.58)		
	Lorc 10 BID	1602	5	3.12				
	Lorc 10 QD	801	0	0.00				

[1]Lorcaserin 10mg BID vs placebo

[2]All lorcaserin vs placebo

Serious Adverse Events in Myocardial infarction SMQ

		Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio[1] (95% CI)	Odds Ratio[2] (95% CI)	Mantel-Haenszel OR[1]	Mantel-Haenszel OR[2]
BLOOM	Pbo	1584	2	1.26	0.50 (0.05, 5.49)	0.50 (0.05, 5.49)	1.74 (0.51, 5.94)	1.35 (0.38, 4.72)
	Lorc 10 BID	1593	1	0.63				
BLOOM-DM	Pbo	252	2	7.94	0.49 (0.04, 5.44)	0.36 (0.03, 3.96)		
	Lorc 10 BID	256	1	3.91				
	Lorc 10 QD	95	0	0.00				
BLOSSOM	Pbo	1601	0	0.00	-	-		
	Lorc 10 BID	1602	5	3.12				
	Lorc 10 QD	801	0	0.00				

[1]Lorcaserin 10mg BID vs placebo

[2]All lorcaserin vs placebo

5. Lorcaserin 10 mg QD Analyses: Broad and Narrow Searches

Adverse Events in Broad[2] CV Search. Lorcaserin 10mg QD vs Placebo

		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio (95% CI)	Mantel-Haenszel OR
BLOOM-DM	Pbo[1]	80	6	75.00	0.69 (0.20, 2.33)	0.64 (0.24, 1.67)
	Lorc 10 QD	95	5	52.63		
BLOSSOM	Pbo	1601	7	4.37	0.57 (0.12, 2.75)	
	Lorc 10 QD	801	2	2.50		

[1]Randomized before amendment 3
[2]Broad Search includes: Haemorrhagic cerebrovascular conditions SMQ, Ischaemic cerebrovascular conditions SMQ and Ischaemic heart disease SMQ

Serious Adverse Events in Broad[2] CV Search. Lorcaserin 10mg QD vs Placebo

		Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio (95% CI)	Mantel-Haenszel OR
BLOOM-DM	Pbo[1]	80	0	0.00	-	1.87 (0.44, 7.92)
	Lorc 10 QD	95	4	42.11		
BLOSSOM	Pbo	1601	4	2.50	0.50 (0.06, 4.47)	
	Lorc 10 QD	801	1	1.25		

[1]Randomized before amendment 3

[2]Broad Search includes: Haemorrhagic cerebrovascular conditions SMQ, Ischaemic cerebrovascular conditions SMQ and Ischaemic heart disease SMQ

Adverse Events in Narrow[2] CV Search. Lorcaserin 10mg QD vs Placebo

		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio (95% CI)	Mantel-Haenszel OR
BLOOM-DM	Pbo[1]	80	5	62.50	0.49 (0.11, 2.11)	0.45 (0.14, 1.52)
	Lorc 10 QD	95	3	31.58		
BLOSSOM	Pbo	1601	5	3.12	0.40 (0.05, 3.42)	
	Lorc 10 QD	801	1	1.25		

[1]Randomized before amendment 3

[2]Broad Search includes: Haemorrhagic cerebrovascular conditions SMQ, Ischaemic cerebrovascular conditions SMQ and Ischaemic heart disease SMQ

Serious Adverse Events in Narrow[2] CV Search

		Total Subjects	Serious AEs	Events / 1000 subjects	Odds Ratio (95% CI)	Mantel-Haenszel OR[1]
BLOOM-DM	Pbo[1]	80	0	0.00	-	2.37 (0.34, 16.39)
	Lorc 10 QD	95	2	21.05		
BLOSSOM	Pbo	1601	2	1.25	1.00 (0.09, 11.04)	
	Lorc 10 QD	801	1	1.25		

[1]Randomized before amendment 3

[2]Broad Search includes: Haemorrhagic cerebrovascular conditions SMQ, Ischaemic cerebrovascular conditions SMQ and Ischaemic heart disease SMQ

6. Preferred terms from SMQ search in Phase 3 trials

STUDY	SUBJID	ARM	PT	SAE	Broad	Narrow
BLOOM	101013	Lorcaserin	Electrocardiogram T wave abnormal	0	1	0
	106048	Lorcaserin	Electrocardiogram ST segment abnormal	0	1	1
	106048	Lorcaserin	Troponin increased	0	1	1
	107147	Lorcaserin	Arteriosclerosis coronary artery	0	1	0
	119084	Lorcaserin	Angina unstable	1	1	0
	119084	Lorcaserin	Coronary artery disease	0	1	0
	122212	Lorcaserin	Electrocardiogram T wave abnormal	0	1	0
	122274	Lorcaserin	Myocardial infarction	0	1	1
	126037	Lorcaserin	Subarachnoid haemorrhage	1	1	0
	126037	Lorcaserin	Subdural haemorrhage	1	1	0
	158036	Lorcaserin	Myocardial infarction	0	1	1
	180003	Lorcaserin	Electrocardiogram T wave abnormal	0	1	0
	180080	Lorcaserin	Coronary artery occlusion	1	1	1
	189070	Lorcaserin	Dysarthria		0	0
	210025	Lorcaserin	Cardiac stress test abnormal	0	1	0
	106036	Placebo	Blood creatine phosphokinase increased	0	1	1
	109022	Placebo	Carotid artery stenosis	0	1	1
	154030	Placebo	Blood creatine phosphokinase increased	0	1	1
	156006	Placebo	Myocardial infarction	1	1	1
	163017	Placebo	Coronary artery disease	0	1	0
	177074	Placebo	Transient ischaemic attack	1	1	1
	188048	Placebo	Coronary artery occlusion	1	1	1
	205109	Placebo	Blood creatine phosphokinase increased	0	1	1
BLOOM-DM	1130-0494	Lorcaserin 10 mg BID	Dysarthria	0	0	0
	1146-0423	Lorcaserin 10 mg BID	Angina unstable	0	1	0
	1146-0423	Lorcaserin 10 mg BID	Coronary artery occlusion	1	1	1
	1146-0423	Lorcaserin 10 mg BID	Coronary artery occlusion	0	1	1
	1159-0041	Lorcaserin 10 mg BID	Blood creatine phosphokinase increased	0	1	1
	1205-0192	Lorcaserin 10 mg BID	Blood creatine phosphokinase increased	0	1	1
	1219-0587	Lorcaserin 10 mg BID	Blood creatine phosphokinase increased	0	1	1
	1226-0289	Lorcaserin 10 mg BID	Blood creatine phosphokinase increased	0	1	1
	1131-0021	Lorcaserin 10 mg QD	Blood creatine phosphokinase increased	0	1	1

STUDY	SUBJID	ARM	PT	SAE	Broad	Narrow
	1131-0061	Lorcaserin 10 mg QD	Coronary artery disease	1	1	0
	1131-0061	Lorcaserin 10 mg QD	Coronary artery disease	0	1	0
	1174-0188	Lorcaserin 10 mg QD	Angina pectoris	1	1	0
	1227-0127	Lorcaserin 10 mg QD	Cerebrovascular accident	1	1	1
	1275-0276	Lorcaserin 10 mg QD	Cerebrovascular accident	1	1	1
	1105-0129	Placebo	Angina pectoris	0	1	0
	1105-0129	Placebo	Angina pectoris	0	1	0
	1130-0114	Placebo	Transient ischaemic attack	0	1	1
	1130-0497	Placebo	Myocardial infarction	1	1	1
	1149-0045	Placebo	Blood creatine phosphokinase increased	0	1	1
	1159-0024	Placebo	Blood creatine phosphokinase increased	0	1	1
	1162-0026	Placebo	Blood creatine phosphokinase increased	0	1	1
	1165-0155	Placebo	Blood creatine phosphokinase increased	0	1	1
	1243-0304	Placebo	Myocardial infarction	1	1	1
	2106-0982	Lorcaserin 10 mg BID	Angina pectoris	0	1	0
	2128-0886	Lorcaserin 10 mg BID	Acute myocardial infarction	1	1	1
	2137-3797	Lorcaserin 10 mg BID	Angina pectoris	1	1	0
	2137-3797	Lorcaserin 10 mg BID	Dysarthria	0	0	0
	2160-1094	Lorcaserin 10 mg BID	Dysarthria	0	0	0
	2196-0343	Lorcaserin 10 mg BID	Acute coronary syndrome	1	1	1
	2203-3369	Lorcaserin 10 mg BID	Myocardial infarction	1	1	1
	2222-1382	Lorcaserin 10 mg BID	Myocardial ischaemia	0	1	0
	2236-0400	Lorcaserin 10 mg BID	Myocardial infarction	1	1	1
	2236-2802	Lorcaserin 10 mg BID	Cerebrovascular accident	0	1	1
BLOSSOM	2250-0033	Lorcaserin 10 mg BID	Myocardial infarction	1	1	1
	2267-1001	Lorcaserin 10 mg QD	Transient ischaemic attack	1	1	1
	2270-2970	Lorcaserin 10 mg QD	Angina pectoris	0	1	0
	2133-1095	Placebo	Carotid arteriosclerosis	0	1	1
	2140-3835	Placebo	Haemorrhage intracranial	1	1	0
	2146-1669	Placebo	Angina unstable	0	1	0
	2146-1669	Placebo	Coronary artery disease	1	1	0
	2167-0962	Placebo	Troponin increased	0	1	1
	2180-3035	Placebo	Transient ischaemic attack	1	1	1
	2182-2834	Placebo	Carotid artery occlusion	0	1	1
	2223-1109	Placebo	Cerebral ischaemia	1	1	1

7. Endpoint Definitions for Sponsor's CV Event Adjudication

A. DEATH CLASSIFICATION

Death will be classified into Cardiovascular, Non-Cardiovascular, or Undetermined

Cardiovascular death includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

1. **Sudden Cardiac Death:** refers to death that occurs unexpectedly and includes the following deaths:
    a. Death witnessed and instantaneous without new or worsening symptoms
    b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms
    c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
    d. Death after unsuccessful resuscitation from cardiac arrest
    e. Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome)
    f. Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available)
2. **Death due to Acute Myocardial Infarction** refers to a death within 30 days after a myocardial infarction (MI) related to consequences seen immediately after the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period), they should be designated by the immediate cause.
3. **Death due to Heart Failure* or Cardiogenic Shock** refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death.

4. **Death due to Stroke**: refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.

5. **Death due to Other Cardiovascular Causes**: refers to death due to a cardiovascular cause not included in the above categories (e.g. dysrhythmia, pulmonary embolism, cardiovascular intervention, aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or non-surgical revascularization, even if "non-cardiovascular" in nature, should be classified as cardiovascular deaths

Non-cardiovascular death is defined as any death not covered by cardiac death or vascular death. Suggested categories* include:

- Pulmonary causes
- Renal causes
- Gastrointestinal causes
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Malignancy (i.e., new malignancy, worsening of prior malignancy)
- Accidental/Trauma
- Hemorrhage, not intracranial
- Suicide
- Non-cardiovascular system organ failure (e.g., hepatic failure)
- Non-cardiovascular surgery
- Other non-cardiovascular, specify: _____

Undetermined Cause of Death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause.

B. MYOCARDIAL INFARCTION

1. Criteria for Acute Myocardial Infarction

The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for myocardial infarction.

For each MI type, one must consider the totality of clinical, electrocardiographic, and cardiac biomarker information to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis.

a. Spontaneous MI

Detection of rise and/or fall of cardiac biomarkers (CK-MB or troponin) with at least one value above the 99th percentile of the upper reference limit (URL)* together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia
- ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]**
- Development of pathological Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

*For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. Total CK may be used only in the absence of troponin and CK-MB data. In the absence of available biomarker data, the CCEC may use other available clinical information (e.g., new thrombotic occlusion of a coronary artery at coronary angiogram in a patient with new acute ST elevation in the distribution of the occluded artery) to determine whether an MI has occurred.

**ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):

- ST elevation
  New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: $\geq$ 0.2 mV in men ($>$ 0.25 mV in men $<$ 40 years) or $\geq$ 0.15 mV in women in leads V2-V3 and/or $\geq$ 0.1 mV in other leads.

- ST depression and T-wave changes
  New horizontal or down-sloping ST depression $\geq$ 0.05 mV in two contiguous leads; and/or new T inversion $\geq$ 0.1 mV in two contiguous leads.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

***Definition of a pathological Q-wave

- Any Q-wave in leads V2-V3 $\geq$ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave $\geq$ 0.03 seconds and $\geq$ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)[a]

[a]The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

Percutaneous Coronary Intervention-Related Myocardial Infarction

For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL* within 48 hours of the procedure are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 x 99th percentile URL* (Troponin or CK-MB $>$ 3 x 99th percentile URL*) are consistent with PCI-related myocardial infarction. MB is the preferred biomarker. Symptoms are not required.

If the cardiac biomarker is elevated prior to PCI, a $\geq$ 50% increase of the value in the second cardiac biomarker sample within 48 hours of the PCI (and Troponin or CK-MB $>$ 3x 99th percentile URL*) and documentation that cardiac biomarker values were decreasing (two samples 3-6 hours apart) prior to the suspected recurrent MI is also consistent with PCI-related myocardial infarction.

c. Coronary Artery Bypass Grafting-Related Myocardial Infarction

For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevation of cardiac biomarkers above the 99th percentile URL within 72 hours of the procedure is indicative of peri-procedural myocardial necrosis. By convention, an increase of biomarkers greater than 5 x 99th percentile URL (Troponin or CK-MB > 5 x 99th percentile URL) plus

- either new pathological Q waves in at least 2 contiguous leads that persist through 30 days or new persistent non-rate related LBBB *or*
- angiographically documented new graft or native coronary artery occlusion or other complication in the operating room resulting in loss of myocardium *or*
- imaging evidence of new loss of viable myocardium

is consistent with CABG-related myocardial infarction. MB is the preferred biomarker.

If the cardiac biomarker is elevated prior to CABG, a ≥ 50% increase of the value in the second cardiac biomarker sample within 72 hours of CABG (and Troponin or CK-MB > 5 x 99th percentile URL) and documentation that cardiac biomarker values were decreasing (two samples 3-6 hours apart) prior to the suspected recurrent MI plus any of the three bullets above is consistent with a periprocedural myocardial infarction after CABG.

Symptoms of cardiac ischemia are not required.

d. Pathological findings of an acute myocardial infarction

Criteria for Silent Myocardial Infarction or Prior Myocardial Infarction (with or without Symptoms)

No evidence of acute myocardial infarction AND any one of the following criteria:

- Appearance of new persistent pathological Q waves. A confirmatory ECG is recommended if there have been no clinical symptoms or history of myocardial infarction.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Pathological findings of a healed or healing myocardial infarction

ECG Changes associated with prior myocardial infarction:

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)[a]
- R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

[a]The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

3. Criteria for Reinfarction

In patients where recurrent myocardial infarction is suspected from clinical signs or symptoms following the initial infarction, recurrent infarction should be diagnosed if there is a $\geq$ 20% increase of the value between a measurement (cardiac biomarker) made at the time of the initial presentation and a further sample taken 3-6 hours later. This value should also exceed the 99th percentile URL.*). This scenario applies to patients enrolled in a clinical trial with an acute myocardial infarction who experience a recurrent myocardial infarction post-enrollment or in patients enrolled in a clinical trial without an acute myocardial infarction but who subsequently experience a myocardial infarction during the course of the trial and a recurrent myocardial infarction.

If cardiac biomarkers are elevated prior to the suspected new MI, there must be decreasing cardiac biomarker values on two samples at least 3 hours apart prior to the suspected new MI in combination with other criteria for reinfarction (ECG, imaging).

If biomarkers are increasing or peak is not reached, then a definite diagnosis of recurrent MI is generally not possible.

4. <u>General Considerations</u>

- For a diagnosis of acute myocardial infarction, elevation of cardiac biomarkers should be present. However, myocardial infarction may be adjudicated for an event that has characteristics (i.e., ischemic symptoms) of a myocardial infarction but which does not meet the strict definition because biomarker or electrocardiographic results are not available (e.g. not measured) or are non-contributory (e.g. may have normalized).

- For procedure-related myocardial infarction, all available biomarker information will be taken into account. Furthermore, in cases where the cardiac biomarker is elevated prior to PCI or CABG.

- Not infrequently, patients with renal disease or congestive heart failure may have elevated cardiac biomarkers. In these circumstances, the Clinical Endpoints Committee must use the totality of the evidence to determine whether the cardiac biomarker elevation or underlying condition represents the primary process or endpoint event.

C. HOSPITALIZATION FOR UNSTABLE ANGINA

Unstable angina requiring hospitalization is defined as

1. Symptoms of myocardial ischemia at rest (chest pain or equivalent) or an accelerating pattern of angina with frequent episodes associated with progressively decreased exercise capacity

AND

2. Prompting an unscheduled visit to a healthcare facility and hospitalization (including chest pain observation units) within 24 hours of the most recent symptoms

AND

3. At least one of the following:

   a. New or worsening ST or T wave changes on resting ECG
      - ST elevation
        New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.

      - ST depression and T-wave changes
        New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

      The above ECG criteria illustrate patterns consistent with myocardial ischemia. It is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

   b. Definite evidence of myocardial ischemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress) that is believed to be responsible for the myocardial ischemic symptoms/signs

   c. Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs

   d. Need for coronary revascularization procedure (PCI or CABG) during the same hospital stay. This criterion would be fulfilled if the admission for myocardial ischemia led to transfer to another institution for the revascularization procedure without interceding home discharge

AND

4. No evidence of acute myocardial infarction

5. General Considerations

- Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of β-blockers, should be considered supportive of the diagnosis of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under category 3, would be insufficient alone to support classification as hospitalization for unstable angina.

- If subjects are admitted with suspected unstable angina, and subsequent testing reveals a non-cardiac or non-ischemic etiology, this event should not be recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for myocardial infarction should not be adjudicated as unstable angina.

- Planned rehospitalization for performance of an elective revascularization in the absence of symptoms at rest prompting admission should not be considered a hospitalization for unstable angina. For example, a patient with stable exertional angina whose admission for coronary angiography and PCI is prompted by a positive outpatient stress test should not be considered a hospitalization for unstable angina.

- A patient who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for unstable angina endpoint.

D. TRANSIENT ISCHEMIC ATTACK AND STROKE

1. Transient Ischemic Attack

Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

2. Stroke

Stroke is an acute symptomatic episode of neurological dysfunction attributed to a vascular cause.

Classification:

A. Ischemic Stroke

Ischemic stroke is defined as an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.

B. Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

C. Undetermined Stroke

Undetermined stroke is defined as a stroke with insufficient information to allow categorization as A or B.

3. General Considerations

- In general a stroke is associated with either symptoms greater than 24 hours in duration, death prior to 24 hours, or imaging evidence of infarction of central nervous tissue
- Intracerebral microhemorrhages will not be considered evidence of a primary hemorrhagic stroke
- For the purpose of adjudication, a stroke known to be ischemic in nature with subsequent transformation to hemorrhagic will be considered an ischemic stroke.

8. Cardiovascular Clinical Endpoints Committee Results Summary (Post-hoc Adjudication), BLOOM and BLOSSOM

Subject ID	Verbatim Term	Preferred Term	Result	Treatment Assignment (Added by Arena)
119084	UNSTABLE ANGINA	Angina unstable	Hosp for UA	Lorc 10 BID
2128-S010	ACUTE MI	Acute myocardial infarction	MI-Spontaneous	Lorc 10 BID
2203-S058	NON Q WAVE MYOCARDIAL INFARCTION	Myocardial infarction	MI-Spontaneous	Lorc 10 BID
2236-S032	MYOCARDIAL INFARCTION	Myocardial infarction	MI-Spontaneous	Lorc 10 BID
2250-S008	MYOCARDIAL INFARCTION	Myocardial infarction	MI-Spontaneous	Lorc 10 BID
192006	ATYPICAL CHEST PAIN	Chest pain	No MI/UA	Lorc 10 BID
2102-S039	CHEST PAIN-MUSCULOSKELETAL	Musculoskeletal chest pain	No MI/UA	Lorc 10 BID
2137-S050	CHEST PAIN OF UNKNOWN ETIOLOGY	Chest pain	No MI/UA	Lorc 10 BID
2137-S083	ANGINA	Angina pectoris	No MI/UA	Lorc 10 BID
2196-S002	PROBABLY ACUTE CORONARY SYNDROME	Acute coronary syndrome	No MI/UA	Lorc 10 BID
2213-S076	NON CARDIAC CHEST PAIN	Non-cardiac chest pain	No MI/UA	Lorc 10 BID
2255-S073	CHEST PRESSURE	Chest discomfort	No MI/UA	Lorc 10 BID
2202-S062	CHEST PAIN NON-CARDIAC	Non-cardiac chest pain	No MI/UA	Lorc 10 QD
2267-S007	TRANSIENT ISCHEMIC ATTACK	Transient iscaemic attack	No Stroke/TIA	Lorc 10 QD
180080	CORONARY ARTERY DISEASE	Coronary artery occlusion	Hosp for UA	Lorc / Pbo
188048	CORONARY ARTERY 95% BLOCK	Coronary artery occlusion	Hosp for UA	Pbo
2146-S090	CORONARY ARTERY DISEASE	Coronary artery disease	Hosp for UA	Pbo
156006	REMOTE LATERAL MYOCARDIAL INFARCTION	Myocardial infarction	MI-Silent	Pbo
146067	CHEST PAIN	Chest pain	No MI/UA	Pbo
2125-S001	CHEST PAIN	Chest pain	No MI/UA	Pbo
2223-S009	CEREBRAL GLOBAL ANOXIA	Cerebral ischaemia	Non CV Death – Pulmonary Stroke Ischaemic	Pbo
132023		Road traffic accident	Non CV Death – Accident/Trauma	Pbo
177074	TRANSIENT ISCHEMIC	Transient	TIA	Pbo

Subject ID	Verbatim Term	Preferred Term	Result	Treatment Assignment (Added by Arena)
	ATTACK	ischaemic attack		
2180-S078	TRNSIENT ISCHEMIC ATTACK	Transient ischaemic attack	TIA	Pbo

Source: NDA 022529 CV Study Report, pg 25 of 54